AJNR

# Persistent enhancement after treatment for cerebral toxoplasmosis in patients with AIDS: predictive value for subsequent recurrence.

J P Laissy, P Soyer, C Parlier, S Lariven, Z Benmelha, V Servois, E Casalino, E Bouvet, A Sibert and F Vachon

*AJNR Am J Neuroradiol* 1994, 15 (9) 1773-1778
http://www.ajnr.org/content/15/9/1773

# Persistent Enhancement after Treatment for Cerebral Toxoplasmosis in Patients with AIDS: Predictive Value for Subsequent Recurrence

Jean Pierre Laissy, Philippe Soyer, Caroline Parlier, Sylvie Lariven, Zakia Benmelha, Vincent Servois, Enrique Casalino, Elisabeth Bouvet, Annie Sibert, François Vachon, and Yves Menu

**PURPOSE:** To determine the predictive imaging (CT and/or MR) features of brain toxoplasmosis recurrences in acquired immunodeficiency syndrome. **METHODS:** The imaging studies of patients with brain toxoplasmosis were retrospectively reviewed. Forty-three patients with significant decrease or disappearance of brain lesions under specific treatment on follow-up imaging examinations were included. MR examinations were performed using T2- and T1-weighted sequences, before and after intravenous administration of gadolinium-DOTA. **RESULTS:** A recurrence occurred in 11 (26%) of 43 cases. Ten (91%) of these 11 patients with recurrence showed focal persistent enhancement after the initial treatment of toxoplasmosis abscess. One of the 11 patients with recurrence showed no persistent enhancement; 3 patients showed persistent enhancement but had no recurrence. **CONCLUSIONS:** Recurrences of brain toxoplasmosis in our series correlated with persistent contrast enhancement. We hypothesize that demonstration of persistent areas of contrast enhancement after treatment for initial toxoplasmosis may be a valuable sign for identifying patients at risk for recurrence.

**Index terms:** Acquired immunodeficiency syndrome (AIDS); Brain, computed tomography; Brain, infection; Brain, magnetic resonance; Toxoplasmosis

*AJNR Am J Neuroradiol* 15:1773–1778, Oct 1994

Toxoplasmosis is by far the most frequent opportunistic brain infection in patients with acquired immunodeficiency syndrome (AIDS) from western European countries, with an incidence estimated to at least 25% (1, 2). The more commonly used treatment of brain toxoplasmosis consists of the association of two specific antibiotics (sulfadiazine, pyrimethamine), followed by a secondary prophylactic monotherapy. However, with the development of retroviral drugs resulting in improved survival rates and despite the use of secondary prophylaxis, several brain toxoplasmosis episodes can recur at any time during the course of the disease (3).

We have undertaken this retrospective study with one goal in mind. We attempted to determine whether imaging features had a prognostic value in predicting recurrences by comparing the initial and follow-up imaging features of the first episode of brain toxoplasmosis in patients with and without recurrences.

## Materials and Methods

Between January 1991 and March 1992, 58 patients referred from the Infectious and Tropical Diseases Department underwent computed tomography (CT) and/or magnetic resonance (MR) imaging for brain toxoplasmosis in our institution. The medical, biological, and imaging charts of these patients were reviewed retrospectively.

Fifteen patients were excluded for the following reasons: 7 owing to incomplete data, 2 because they were suspected of associated brain cryptococcosis on the basis of positive antigen blood titer and culture, and 6 because there was insufficient proof to ensure that brain lesions were not of another cause. Of these 6 patients, 3 died without long enough follow-up to document resolution of the lesions, and 3 patients did not undergo the routine follow-up clinical, biological, and imaging protocol. Forty-three patients met these preliminary inclusion criteria: (*a*)

Received April 30, 1993; accepted after revision January 28, 1994.

Fom the Departments of Radiology (J.P.L., P.S., C.P., Z.B., V.I., A.S., Y.M.) and Tropical and Infectious Diseases (S.L., E.C., E.B., F.V.), Hôpital Bichat, Paris, France.

Address reprint requests to Jean-Pierre Laissy, MD, PhD, Department of Radiology, Hôpital Bichat, 46 rue Henri Huchard, 75877 Paris cedex 18, France.

AJNR 15:1773–1778, Oct 1994 0195-6108/94/1509–1773

neurologic manifestations such as headache, focal deficits, epilepsy, and/or fever; (*b*) CD4 counts less than 200 cells per cubic millimeter; (*c*) no previous brain toxoplasmosis; (*d*) positive cerebrospinal fluid serology for toxoplasmosis, as determined by either initial negative titers that became positive at follow-up or rising titers at follow-up confirmed by increasing serology titers for toxoplasmosis (these criteria were used for both initial diagnosis and diagnosis of recurrence); (*e*) negative blood and cerebrospinal fluid titers for cryptococcosis or other viral (cytomegalovirus), bacterial (mycobacterium, nocardia), or mycotic infections (candida) initially and during follow-up, contemporarily to imaging examinations (these studies were routinely performed in all patients); (*f*) significant and durable improvement on clinical and imaging follow-up under antitoxoplasmosis therapy (return to a normal neurologic status, no fever, and resolution of edema and mass effect, regression, or disappearance of the abscess at CT or MR imaging) (three patients within this group had initial unfavorable response to therapy; stereotactic biopsy confirmed toxoplasmic abscesses in these three cases); and (*g*) a follow-up period of at least 1 year (the range of follow-up times available from shortest to longest time period was 12 to 26 months for a mean ± SD of 16.5 ± 2.8 months). The chart reviews from the initial diagnosis until the end of the follow-up period were studied in these 43 AIDS patients (11 of them were found to have had at least one recurrence).

Initial treatment regimen included in all patients at least a bitherapy with sulfadiazine (100 mg/kg per day) and pyrimethamine (3 mg/kg per day). After initial treatment, all the patients were maintained on secondary prophylaxis including the two drugs at half dose until normalization at imaging, then only one drug (pyrimethamine 1.5 mg/kg per day).

Clinical signs were noted, and biological signs were basically recorded: CD4 lymphocyte levels per cubic millimeter and CD4/CD8 ratio; viral replication signs ($P_{24}$ antigenemia, $\beta$2 microglobulinemia); positive serology for toxoplasmosis; and time course of the radiographic response to therapy. Follow-up examination intervals were evaluated according to a routine follow-up imaging protocol. Imaging studies were performed in all cases at the time of diagnosis, then at 2 weeks, 4 weeks, 2 months, and 6 months after initiation of therapy. Intermediate examinations were performed in cases of new neurologic symptoms and/or fever without evident origin.

Initial imaging examination was performed within a 24-hour interval after the onset of symptoms. CT was the first examination in 21 patients and the only one in 12 of them. CT was performed before and after intravenous administration of 120 mL of contrast medium (iodine 38 g/100 mL).

MR examinations were performed on a 1-T magnet with the use of a quadrature emitting-receiving surface coil. It was the initial examination for 22 patients. It included at least axial spin-echo T2-weighted 2200/20–90/1 (repetition time /echo time /excitations) and T1-weighted 450/15/2 sequences before and T1-weighted imaging after intravenous injection of 0.1 mmol/kg of Gd-DOTA.

**TABLE 1: Estimation of edema and mass effect**

| | Recurrence n = 11 | No recurrence n = 32 |
|---|---|---|
| Edema | | |
| Absent | 2 (18%) | 9 (28%) |
| Less than the lesion diameter | 5 (46%) | 8 (25%) |
| Equal to the lesion diameter | 4 (36%) | 9 (28%) |
| Greater than the lesion diameter | 0 | 6 (19%) |
| Mass effect | | |
| Absent | 7 (64%) | 19 (59%) |
| Displacement of one of the following structures: Cortical gyri Ventricle Midline | 2 (18%) | 6 (19%) |
| Displacement of two of the above structures | 1 (9%) | 3 (9%) |
| Displacement of the three structures | 1 (9%) | 4 (13%) |

Images were interpreted by three independent radiologists, without knowledge of clinical and biological status. All the follow-up examinations were studied. Imaging data then were correlated with clinical and biological data.

### *Image Analysis*

The analysis of MR and CT abnormalities included the number of lesions per patient, shape (nodular or ring enhancement), size (larger or smaller than 2 cm), and location. Unenhanced CT attenuation and MR signal intensity as well as the importance of contrast enhancement were studied. Brain involvement ("edema") around the lesions and the mass effect were visually quantified arbitrarily (Table1). These signs were recorded for the initial imaging procedure and for follow-up. Brain sequelae were recorded, including the description of encephalomalacia, hemorrhagic lesions, and focal residual-contrast enhancement.

Recurrence was documented when, after initial improvement on CT and MR images under treatment (resolution of edema, regression or disappearance of the abscess), there was a new lesion or a recurrence in the same area. This recurrence was confirmed by the elevation of toxoplasmosis antigen titers in the cerebrospinal fluid and serum and the absence of elevated titers for other brain infections.

### *Statistical Analysis*

The two groups of patients, 32 without and 11 with recurrences, were compared. The clinical and imaging data were cross-matched between the group without and the group with recurrence.

A statistical analysis using the nonparametric Wilcoxon rank sum test was performed to test the significance of the differences observed in clinical, laboratory, and imaging data between the two groups. A $P$ value less than .05 was considered significant.

## Results

The whole population included 35 men and 8 women, aged 23 to 69 years (mean, 35.6). The mean time interval between human immunodeficiency virus diagnosis and brain toxoplasmosis was 2.1 years. Toxoplasmosis was the inaugural manifestation of AIDS in 25 patients. Thirteen patients had previous or concomitant AIDS opportunistic infections such as *Pneumocystis carinii* pneumonia (n = 12) and cytomegalovirus retinitis (n = 2). Six patients had Kaposi sarcoma at initial presentation or during the follow-up period; 6 had tuberculosis. Associated brain lesions observed during the follow-up were progressive multifocal leukoencephalopathy in 1 patient, human immunodeficiency virus encephalopathy in 3, and type B lymphoma in 1.

All the patients had CD4 counts lower than 100 cells per cubic millimeter (3 to 95; average, 29.5). Time interval between initial diagnosis and treatment of cerebral toxoplasmosis and detection of recurrence in the 11 patients ranged from 6 to 12 months (mean, 8.8 ± 2.1 months).

### *Clinical Differences between the Two Groups of Patients*

Patients with recurrences did not exhibit significantly different clinical and biological patterns from the other group of patients. However, patients with recurrences were mostly subjects in whom toxoplasmosis was the initial event of human immunodeficiency virus conversion (8/11 versus 17/32; $P < .05$). The CD4 level was lower than that of patients without recurrences (mean ± SD, 14.4 ± 11.7 versus 32.5 ± 15.6; $P < .01$).

### *Imaging Differences between the Two Groups of Patients*

The population with recurrences exhibited fewer lesions on average and more ring-enhancing lesions at the initial diagnosis, but this observation was not significant. The lesion size was similar between the two groups as well as the frequency and importance of mass effect and edema (Tables 1 and 2). The time course of the radiographic response to therapy was similar between the two groups.

**TABLE 2: Initial and follow-up imaging patterns of patients with and without recurrences**

| | Recurrence (n = 11) | No recurrence (n = 32) | Significance |
|---|---|---|---|
| Initial | | | |
| Average number of lesions | 2.2 | 3.8 | NS |
| Size | | | |
| <2 cm | 73% | 76% | NS |
| >2 cm | 27% | 24% | NS |
| Shape | | | |
| Solid | 57% | 71% | NS |
| Ring-enhancing | 43% | 29% | NS |
| Follow-up | | | |
| Time course of the radiographic response to therapy (days) | 28.9 ± 10.6 | 25.8 ± 6.6 | NS |
| Sequelae | 11 (100%) | 21 (66%) | $p < .01$ |
| Encephalomalacia | 0% | 8 (25%) | $p < .05$ |
| Encephalomalacia plus hemorrhage | 1 (9%) | 7 (22%) | $p < .05$ |
| Hemorrhage | 0% | 3 (9%) | $p < .05$ |
| Encephalomalacia plus persistent enhancement | 7 (64%) | 2 (6%) | $p < .01$ |
| Persistent enhancement | 3 (27%) | 1 (3%) | $p < .01$ |

Note.—NS indicates not significant.

Thirty-one (72%) of 43 patients exhibited brain sequelae. Twelve of them exhibited areas of encephalomalacia, and 13 (30%) persistent focal enhancement in the subcortical regions and/or in the vascular territory supplied by striate arteries (Fig 1). Hemorrhagic sequelae were observed in 10 (23%) patients.

Persistent enhancement areas were significantly correlated to the incidence of recurrences ($P < .01$), but areas of encephalomalacia were not. Persistent enhancement was observed in 10 (91%) of 11 patients with recurrence (Fig 1–3,), whereas it was only observed in 3 (9%) of the 32 patients without recurrence (Table 2). The last case was a local recurrence observed in an hemorrhagic area that could obscure underlying persistent residual contrast enhancement. This was the only patient with hemorrhagic form of toxoplasmosis in this group (9%) compared with the 9 (28%) of 32 cases in the group without recurrences ($P < .01$). No recurrence was observed in patients without brain sequelae.

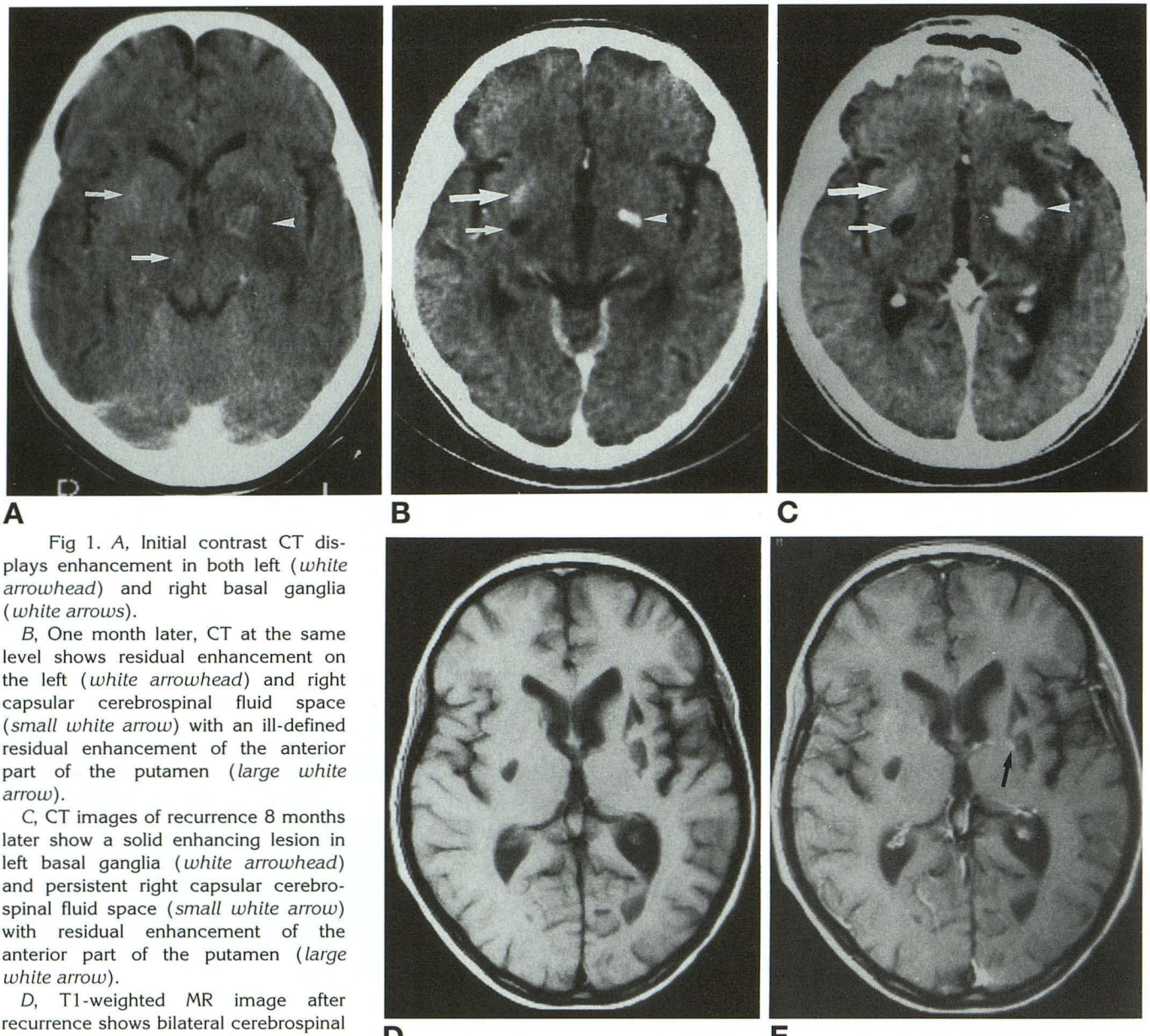


Fig 1. *A,* Initial contrast CT displays enhancement in both left (*white arrowhead*) and right basal ganglia (*white arrows*).

*B,* One month later, CT at the same level shows residual enhancement on the left (*white arrowhead*) and right capsular cerebrospinal fluid space (*small white arrow*) with an ill-defined residual enhancement of the anterior part of the putamen (*large white arrow*).

*C,* CT images of recurrence 8 months later show a solid enhancing lesion in left basal ganglia (*white arrowhead*) and persistent right capsular cerebrospinal fluid space (*small white arrow*) with residual enhancement of the anterior part of the putamen (*large white arrow*).

*D,* T1-weighted MR image after recurrence shows bilateral cerebrospinal fluid spaces in the basal ganglia as confirmed on T2-weighted images (not shown) and attributed to Virchow-Robin space dilation as previously described in cryptococcosis.

*E,* After injection persistent enhancement of the internal part of dilated Virchow-Robin spaces in the left putamen (*small black arrow*).

## Discussion

Several investigators have described the imaging features of brain toxoplasmosis in AIDS (4–9); some of them described toxoplasmosis sequelae (10). Few papers reported on toxoplasmosis recurrences, focusing on their clinical aspects (2, 3). It has been observed that patients who relapse after receiving an adequate course of therapy often develop new lesions in areas of the brain previously free of infection (2). The results of the present study demonstrate that three main factors influence features of brain toxoplasmosis recurrences: the delay between AIDS and toxoplasmosis, the CD4 count level, and the residual focal enhancement. Furthermore, we observed that local recurrences at a site of previous infection are frequent, usually occurring in cases with persistent enhancement. In our series, toxoplasmosis inaugural for AIDS was frequently associated with

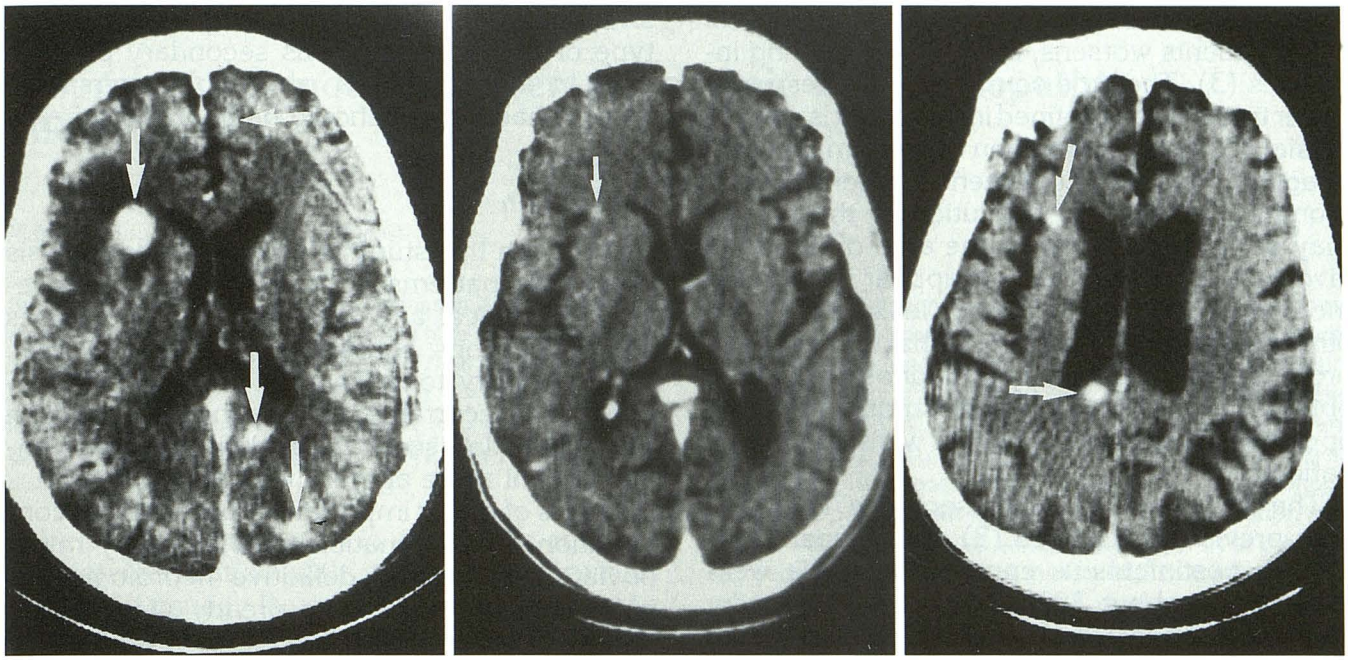


Fig 2. *A*, CT exhibits four nodular toxoplasmosis abscesses of different sizes, one at the anteriormost part of right external capsule, two in the left occipital lobe, and one in the left frontal lobe (*large white arrows*).

*B*, One month after treatment residual persistent enhancement of the right external capsule (*small white arrow*) is present.

*C*, Seven months later local nodular recurrence associated with a new lesion in the splenium of the corpus callosum (*large white arrows*).

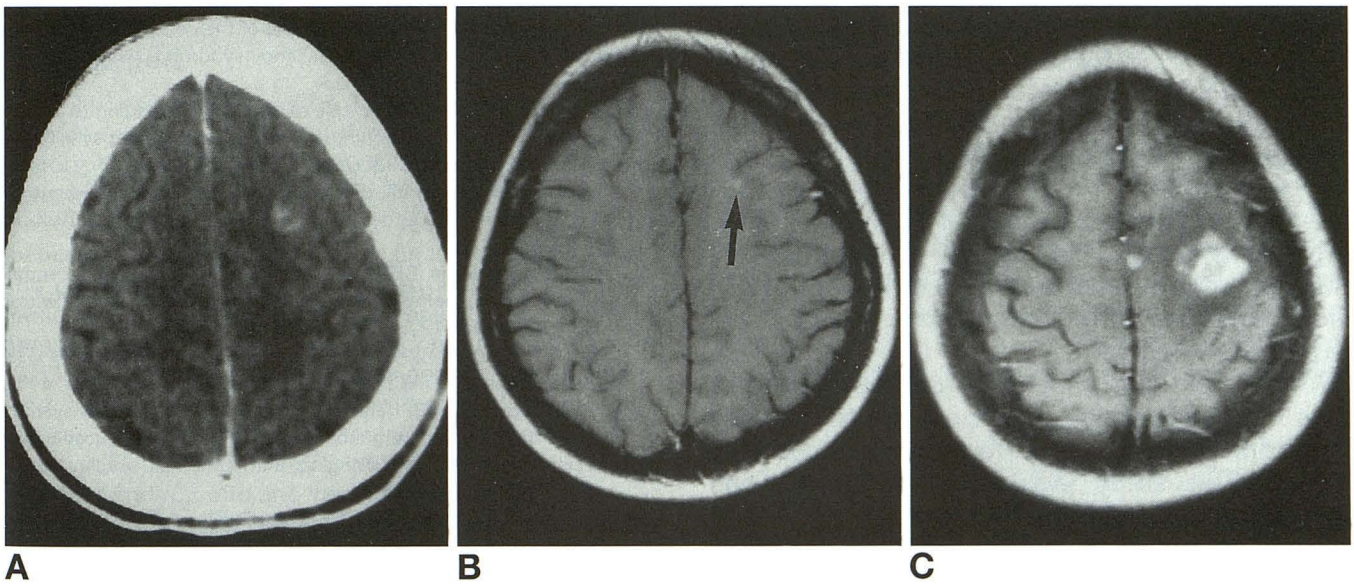


Fig 3. *A*, Initial contrast CT examination displays a toxoplasmic abscess in the left frontal lobe.

*B*, Postcontrast MR examination after 1 month of treatment exhibits persistent enhancement (*black arrow*).

*C*, Postcontrast MR image 1 year later shows recurrence in the same area.

low CD4 levels. As immunocompetence of these patients worsens, the risk of relapsing increases (3). The time course of initial response under treatment as defined in this study is controversial. Complete resolution of abnormalities on imaging may vary between 3 weeks and 6 months. The time to resolution of the lesions may of course depend on the area of the brain involved; superficial lesions appear to respond more quickly than do deeper lesions (2). Another limitation of this study is that no histologic proof is available; the final diagnosis was thus obtained from titers for toxoplasmosis and other opportunistic infections, which were done in all patients.

The frequency of brain sequelae is higher than previously reported (3). The areas attributed to postinfectious encephalomalacia were observed in about 20% of cases in our study; they were described as specific signs of brain cryptococcosis in another group of AIDS patients (11). It is possible that cryptococcosis accounts for infection in some of these patients; it is either a primary infection or a cause of recurrent imaging findings. However, no patient in our series had positive blood or CSF antigen titer or culture for cryptococcosis at initial diagnosis or at follow-up. These areas could also be considered dilated Virchow-Robin spaces (12). Furthermore, we think that residual persistent contrast enhancement can either correspond to active toxoplasmosis abscesses or be located in Virchow-Robin spaces, and we hypothesize that they correspond to active tachyzoite sites, accounting for a strong probability of recurrences. Regardless of the mechanism of these abnormalities, recurrences are far more frequent in such cases than in those in which no enhancing sequelae are present.

It is well known that secondary prophylaxis does not seem effective against the recurrence of toxoplasmosis (2). However, because this retrospective study included a heterogeneous population of patients, one cannot draw any conclusion.

Sequelae occur mainly in patients with severe immunodeficiency (3). Thus, they are at risk for recurrences, although they are given an effective secondary antitoxoplasmosis prophylaxis. Recurrences occur frequently at the site of a previous lesion, especially when a residual contrast enhancement remains. Recurrences are indeed observed in this group of patients, which raises the question of the use of more aggressive antibiotic therapies. The question of the type of treatment given as secondary prophylaxis in those subjects who exhibit persistent focal enhancement should be addressed.

## Conclusion

Although this study is a preliminary analysis of specific patterns of brain toxoplasmosis related to clinical and imaging profiles, it raises some questions and suggests further studies. One might try to resolve the problem of toxoplasmosis recurrence by treating patients with brain sequelae such as residual persistent enhancement more aggressively than others.

This is of major importance, because the continuation of combination antibiotherapy might obviate serious and definitive neurologic impairment in those patients already affected by a variety of other morbidities.

## References


1. Navia BA, Petito CK, Gold JWM, Cho ES, Jordan BD, Price RW. Cerebral toxoplasmosis complicating the acquired immune deficiency syndrome: clinical and neurological findings in 27 patients. *Ann Neurol* 1986;19:224–238
2. Luft BJ, Remington JS. Toxoplasmosis encephalitis in AIDS. *Clin Infect Dis* 1992;15:211–222
3. Porter SP, Sande MA. Toxoplasmosis of the central nervous system in the acquired immunodeficiency syndrome. *N Engl J Med* 1992;327:1643–1648
4. Ciricillo SF, Rosenblum ML. Use of CT and MR imaging to distinguish intracranial lesions and to define the need for biopsy in AIDS patients. *J Neurosurg* 1990;73:720–724
5. Levy RM, Rosenblum ML, Perret LV. Neuroradiologic findings in AIDS: a review of 200 cases. *AJNR Am J Neuroradiol* 1986;7: 833–839
6. Levy RM, Bredesen DE, Rosenblum ML. Opportunistic central nervous system pathology in patients with AIDS. *Ann Neurol* 1988;23(suppl):7–12
7. Olsen WL, Longo FM, Mills CM, Norman D. White matter disease in AIDS: findings at MR imaging. *Radiology* 1988;169:445–448
8. Post MJD, Sheldon JJ, Hensley GT, et al. Central nervous system disease in acquired immunodeficiency syndrome: prospective correlation using CT, MR imaging, and pathologic studies. *Radiology* 1986;158:141–148
9. Ramsey RG, Geremia GK. CNS Complications of AIDS; CT and MR findings. *AJR Am J Roentgenol* 1988;151:449–454
10. Post MJD, Kursunoglu SJ, Hensley GT, Chan JC, Moskowitz LB, Hoffman TA. Cranial CT in acquired immunodeficiency syndrome: spectrum of diseases and optimal contrast enhancement technique. *AJNR Am J Neuroradiol* 1985;6:743–754
11. Tien RD, Chu PK, Hesselink JR, Duberg A, Wiley C. Intracranial cryptococcosis in immunocompromised patients: CT and MR Imaging. *AJNR Am J Neuroradiol* 1991;12:283–289
12. Braffman BH, Zimmerman RA, Trojanowski JQ, Gonatas NK, Hickey WF, Schlaepfer WW. Brain MR: pathologic correlation with gross and histopathology: lacunar infarction and Virchow-Robin spaces. *AJNR Am J Neuroradiol* 1988;9:621–628